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Application of machine learning in affordable and accessible insulin management for type 1 and 2 diabetes: A comprehensive review

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ABSTRACT

Proper insulin management is vital for maintaining stable blood sugar levels and preventing complications associated with diabetes. However, the soaring costs of insulin present significant challenges to ensuring affordable management. This paper conducts a comprehensive review of current literature on the application of machine learning (ML) in insulin management for diabetes patients, particularly focusing on enhancing affordability and accessibility within the United States. The review encompasses various facets of insulin management, including dosage calculation and response, prediction of blood glucose and insulin sensitivity, initial insulin estimation, resistance prediction, treatment adherence, complications, hypoglycemia prediction, and lifestyle modifications. Additionally, the study identifies key limitations in the utilization of ML within the insulin management literature and suggests future research directions aimed at furthering accessible and affordable insulin treatments. These proposed directions include exploring insurance coverage, optimizing insulin type selection, assessing the impact of biosimilar insulin and market competition, considering mental health factors, evaluating insulin delivery options, addressing cost-related issues affecting insulin usage and adherence, and selecting appropriate patient cost-sharing programs. By examining the potential of ML in addressing insulin management affordability and accessibility, this work aims to envision improved and cost-effective insulin management practices. It not only highlights existing research gaps but also offers insights into future directions, guiding the development of innovative solutions that have the potential to revolutionize insulin management and benefit patients reliant on this life-saving treatment.

1. Introduction

According to the World Health Organization (WHO), diabetes directly accounted for approximately 1.5 million deaths in 2019, nearly half of which occurred before the age of 70. As per the American Diabetes Association (ADA), diabetes ranked as the seventh leading cause of death in the United States (US), with 87,647 death certificates attributing to it. Globally, an estimated 463 million individuals were living with diabetes in 2019, with this chronic disease significantly contributing to costly and debilitating complications such as cardiovascular disease, retinopathy, neuropathy, nephropathy, and neurocognitive decline [1]. Notably, diabetes can reduce life expectancy by 4 to 10 years for individuals aged 40 to 60 and independently elevate mortality risk [1]. As reported by Parker et al. [2], the total annual expenditure for diabetes in 2022 reached $412.9 billion, comprising $306.6 billion in direct medical costs and $106.3 billion in indirect costs associated with diabetes. These indirect costs include increased absenteeism, reduced productivity for employed individuals, decreased productivity for those not in the workforce, inability to work due to disease-related disability, and lost productivity due to premature deaths.

Individuals diagnosed with type 1 diabetes (T1D) rely on insulin to ensure their survival, maintain optimal blood glucose levels, and mitigate the risk of complications. Similarly, individuals suffering from type 2 diabetes (T2D) turn to insulin when their oral medications lose efficacy as the disease progresses, aiming to regulate blood glucose levels and prevent complications [1,3,4]. The groundbreaking discovery of insulin in 1921 stands as an unparalleled milestone in medical history, revolutionizing the treatment landscape for individuals with diabetes [5]. The profound impact of insulin therapy on crucial aspects such as well-being, weight restoration, energy levels, and the prevention of diabetic ketoacidosis cannot be overstated [5]. Among the 30.3 million Americans affected by diabetes, approximately 7.4 million individuals rely on one or more forms of insulin for managing their condition [6]. While progress in insulin therapy and delivery methods has significantly

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improved outcomes and lessened the daily treatment burden over time, the global cost of insulin has seen a staggering increase [7]. The escalating prices of insulin impose a substantial financial burden on patients. Notably, the US faces a substantial surge in insulin expenses, with commonly used analog insulin forms costing ten times more than in other developed countries [8]. Remarkably, expenditures on insulin in the US have tripled over the past decade, increasing from $8 billion in 2012 to $22.3 billion in 2022 [2]. In comparison to other countries, the US exhibited markedly higher prices in each insulin category. Fig. 1 illustrates the average price per standard unit by insulin type [9]. On a global scale, there is a significant price gap between human insulin and the pricier insulin analog formulations. Over time, there has been a rising trend in the utilization of insulin analogs compared to regular human insulin, particularly in more developed regions of the world [10,11]. Recognizing the urgency of this medical situation, the gravity of the issue is underscored by governmental intervention, exemplified by the enactment of President Biden's Inflation Reduction Act [12,13]. This legislation targets the escalating costs of crucial medical treatments, including insulin.

The WHO's health systems framework emphasizes the importance of a well-functioning system that provides equitable access to essential medical products, vaccines, and technologies with assured quality, safety, efficacy, and cost-effectiveness, while promoting their scientifically sound and cost-effective use [14]. However, millions of individuals with diabetes around the world continue to encounter challenges in obtaining life-saving insulin [15]. Accessing insulin is becoming an increasingly significant public health concern, especially for those who rely on it for their survival and for them lack of access leads to hyperglycemia within a matter of days or weeks [15,16]. Uninterrupted access to insulin is crucial for patients due to the potential acute health risks, such as high blood sugar, including heart disease, kidney failure, blindness, nerve damage, amputations, and potentially fatal diabetic ketoacidosis (DKA) [15,17]. The US faces significant challenges when it comes to the affordability and accessibility of insulin, including the list price escalation, inconsistent insurance coverage, complexity of the insulin supply chain and pricing mechanisms, limited competition within the insulin market, and a lack of readily available generic alternatives ([18]; The Lancet Diabetes [14,15,19–21]).

Diabetes can be effectively controlled through a balanced combination of a healthy diet, regular physical activity, and appropriate medication as required [4,22]. The rising cost of insulin and costs associated with diabetes-related supplies have led to subsequent underuse [4,23,24]. It is shown that in 2017 at the Yale diabetes center, a quarter of patients admitted to using less insulin than prescribed, discontinuing insulin use, or struggling to fulfill their insulin prescriptions, all of which are linked to poor glycemic control [23,25]. It is estimated that one-fourth of the 7 million Americans who require insulin have encountered difficulties affording their medication; consequently, they have resorted to using insulin less frequently than prescribed and injecting expired doses, leading to worsened glycemic control, hospitalizations due to DKA, and even death [26].

Artificial intelligence (AI), particularly machine learning (ML), possesses the ability to handle and process vast amounts of information in a variety of applications such as manufacturing [27], agriculture [28], healthcare [29–33], and transportation [34] in capacities of predictive and prescriptive analytics. AI and ML have transformed the management of complex diseases like diabetes and cancer by enabling the development of decision-support tools and applications. These tools aid in early detection and diagnosis, personalized treatment planning, predictive analytics for disease progression, drug discovery and development, remote monitoring and management, and clinical decision support [35]. Overall, AI and ML enhance patient outcomes and reduce healthcare costs by leveraging data-driven insights to optimize care delivery [36–38]. The following provides an overview of the review papers focusing on the application of AI and ML in diabetes and insulin management (Table A1 in Appendix A contains the overview of each review paper, along with their corresponding categorization points):

1.1. Prediction, diagnosis, and management of diabetes

Afsaneh et al. [39] provided a comprehensive review of the recent applications of ML and deep learning (DL) models in the prediction, diagnosis, and management of diabetes. Chaki et al. [40] presented a systematic review that provides a comprehensive analysis of the latest techniques and advancements in the field of diabetes detection, diagnosis, and self-management using ML and AI. Nomura et al. [37] explored the potential of AI and ML in the field of diabetes management and prediction. They discussed the current advancements in AI technologies that mimic the "hidden tips of treatments by a specialist," such as fine-tuning insulin dose, and presents examples of AI-based medical devices approved by the US Food and Drug Administration (FDA) for diabetes management. Gautier et al. [41] presented a review that focuses on the potential of AI in understanding and managing diabetes including AI and understanding risk factors; AI and improving diagnosis; AI and understanding diabetes pathophysiology; AI and understanding the natural history of diabetes; and AI and managing diabetes. Broome et al. [42] discussed the policy implications of AI and ML in diabetes management and identified key challenges that must be overcome to leverage ML to its full potential, such as secure and trustworthy data sharing, collaboration between clinicians and developers, and the need for models that balance public good with profitability. The study of Fatima and Pasha [43] was a survey of ML algorithms for disease diagnostic, emphasizing the importance of computer aided diagnosis in medical imaging and the need for accurate diagnostic systems to avoid misleading medical treatments. The survey covered various ML techniques used in different diseases, including cancer, heart disease, and diabetes. Donsa et al. [44] focused on therapy process and identified open problems and challenges for the personalization of diabetes therapy using computerized decision support system (DSS) and ML.

1.2. Optimizing insulin usage/delivery

Burnside et al. [45] discussed the role of AI and ML in optimizing insulin dosing strategies and developing personalized prediction tools.

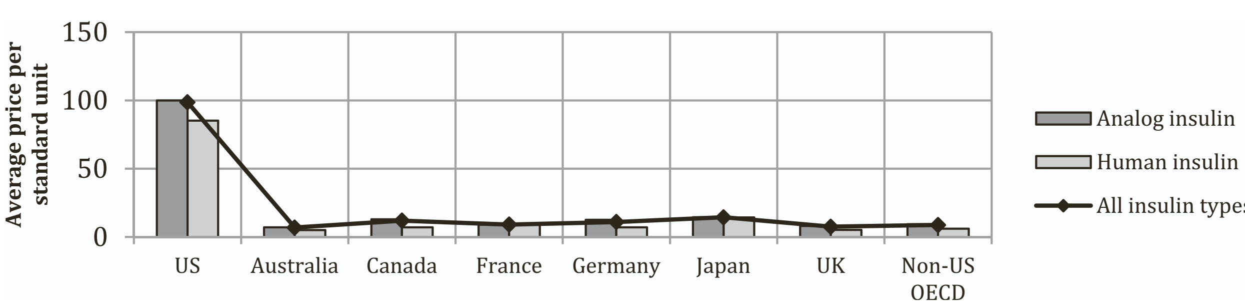


Fig. 1. Average price per standard unit by insulin type [9].

Thomsen et al. [46] provided an overview of methods used for basal insulin dose guidance supporting titration of people with T2D, and categorizing these methods by characteristics, effect, and user experience. Vettoretti et al. [47] reviewed the latest AI methodologies and continuous glucose monitoring (CGM) sensor utilization for decision support in advanced T1D management, including personalized insulin calculations, adaptive parameter tuning, and glucose prediction. Forlenza [48] discussed the use of AI and automated decision support to improve diabetes outcomes using multiple daily injections therapy.

1.3. Predicting glucose levels and optimizing usage of insulin

Makroum et al. [49] conducted a systematic review and explored the potential of ML and smart devices in managing diabetes and predicting postprandial glycemic status and adapting the delivery of insulin bolus (IB). Additionally, it emphasized the integration of AI with smart devices, wearables, smartphones, and sensor technology to build a machine capable of supervising and monitoring people with diabetes continuously. Dankwa-Mullan et al. [50] explored various AI-powered tools and technologies, such as automated retinal screening, patient self-management tools, glucose sensors, and insulin pumps. The paper also highlighted the benefits of AI in diabetes care, including improved patient and clinician engagement, personalized insights, and better control of blood glucose levels.

1.4. Education

Li et al. [51] provided an overview of the potential of AI in diabetes education and management. They discussed various AI applications in diabetes care, including personalized education, glucose monitoring, and insulin delivery.

1.5. Predicting glucose levels

Zale and Mathioudakis [52] reviewed the clinical evidence for the role of ML models in predicting hospitalized patients' glucose trajectory. They concluded that advanced ML models using large Electronic Health Record (EHR) datasets with large numbers of clinical predictors achieve greater predictive accuracy for glucose than more traditional regression modeling techniques in hospitalized patients. Alhaddad et al. [53] focused on the use of ML algorithms in non-invasive blood glucose monitoring using wearable sensors. They discussed the challenges of acquiring enough comprehensive data to train and test models that can be generalized to a wider population, as well as the need for larger studies with more participants to account for inter-individual differences and establish better validation of proposed solutions. Woldaregay et al. [54,55] identified, assessed, and analyzed the state-of-the-art ML strategies in blood glucose anomaly classification and detection including glycemic variability, hyperglycemia, and hypoglycemia in people with T1D. The review covered ML approaches pertinent to personalized DSSs and blood glucose alarm events applications in T1D.

1.6. Predicting hypoglycemia

Mujahid et al. [56] reviewed the literature on ML techniques for hypoglycemia prediction in diabetic patients, focusing on studies published in the last five years. Tyler and Jacobs [57] provided a comprehensive review of computational, and AI based DSSs for managing T1D. The DSSs were categorized into two groups: those recommending insulin adjustments and those predicting and preventing hypoglycemia. The review examined the AI techniques employed in each system, evaluated their performance, and discussed potential applications in managing T1D. Wearable CGM sensors are transforming the treatment of T1D by providing real-time information on blood glucose levels and rate of change. This data is crucial for determining insulin dosage and predicting adverse events.

1.7. Predicting diabetes complications

Ellahham [58] explored the potential of AI in revolutionizing the diagnosis and management of diabetes. It highlighted the use of predictive models and algorithms to assess the risk of developing complications and predict the onset of diabetes. Kavakiotis et al. [59] reviewed how ML and data mining techniques have been used in predicting and diagnosing diabetes, studying diabetic complications, exploring the genetic background and environment of the disease, and improving healthcare and management for diabetes patients. They emphasized the popularity of prediction and diagnosis studies and the dominance of supervised learning approaches.

1.8. Utilizing various ML techniques/AI tools in diabetes research

Abhari et al. [60] reviewed the use various AI techniques, such as ML, natural language processing (NLP), robotics, fuzzy logic (FL), expert systems (ES), knowledge base (KB), and the mix of two or more methods (multi-methods), and how they in T2D care including disease probability prediction, screening, diagnosis, treatment guidance, and complication management. Singla et al. [61] discussed the use of ML and AI in the management of chronic diseases, specifically diabetes. The paper suggested that careful data collection and a gradual transition from supervised to unsupervised ML can help overcome challenges. Indoria and Rathore [62] compared the performance of two ML techniques, Artificial Neural Network (ANN) and Bayesian network, in the classification of diabetes and cardiovascular diseases. Rigla et al. [63] discussed the transformation of diabetes management with the addition of CGM and insulin pump data, as well as the availability of a wide variety of physiological variables through wearable devices. They highlighted the most frequently used AI tools in healthcare, including neural networks, fuzzy logic, and expert systems, providing applied examples in diabetes management.

While existing literature provide ample evidence supporting the effectiveness of ML models in certain domains, particularly in predicting and treating diabetes (Contreras & Vehdi, 2018), a notable gap remains, prompting the offering of a unified review on the latest efforts and advances in data-driven modeling and supervised ML techniques employed in affordable and accessible insulin management for diabetes. Supervised ML involves training models using labeled data or input/output pairs to predict future outcomes, aiming to approximate a function that can effectively predict outputs for new inputs [38]. The paper identifies crucial themes, addresses the limitations of current methods, and proposes potential avenues for future research to yield more insightful outcomes in this domain.

2. Materials and methods

This review aims to provide a comprehensive overview of the application of supervised ML in the management of insulin for diabetes. This review seeks to gather a thorough understanding of how supervised ML techniques can be effectively utilized in addressing the challenges related to insulin accessibility and affordability in diabetes management. The methodology imbedded to select the recent literature developments concerning the topics of data driven and supervised ML models for effective and affordable insulin treatment are discussed here. Papers from 2015 to 2023 were reviewed due to the increase in publications during this time span. The complete list of keywords is presented in Fig. 2.

This search was narrowed down to 350 papers in English, focusing on the intersection of ML and diabetes management from Google Scholar and PubMed search engines. The search strategy excluded papers that examined alternative anti-diabetic medications, predictions and diagnoses of diabetes, unsupervised learning, reinforcement learning (RL), as well as papers solely focused on lifestyle-related diabetes management. Ultimately, a total of 153 papers were selected for inclusion in this

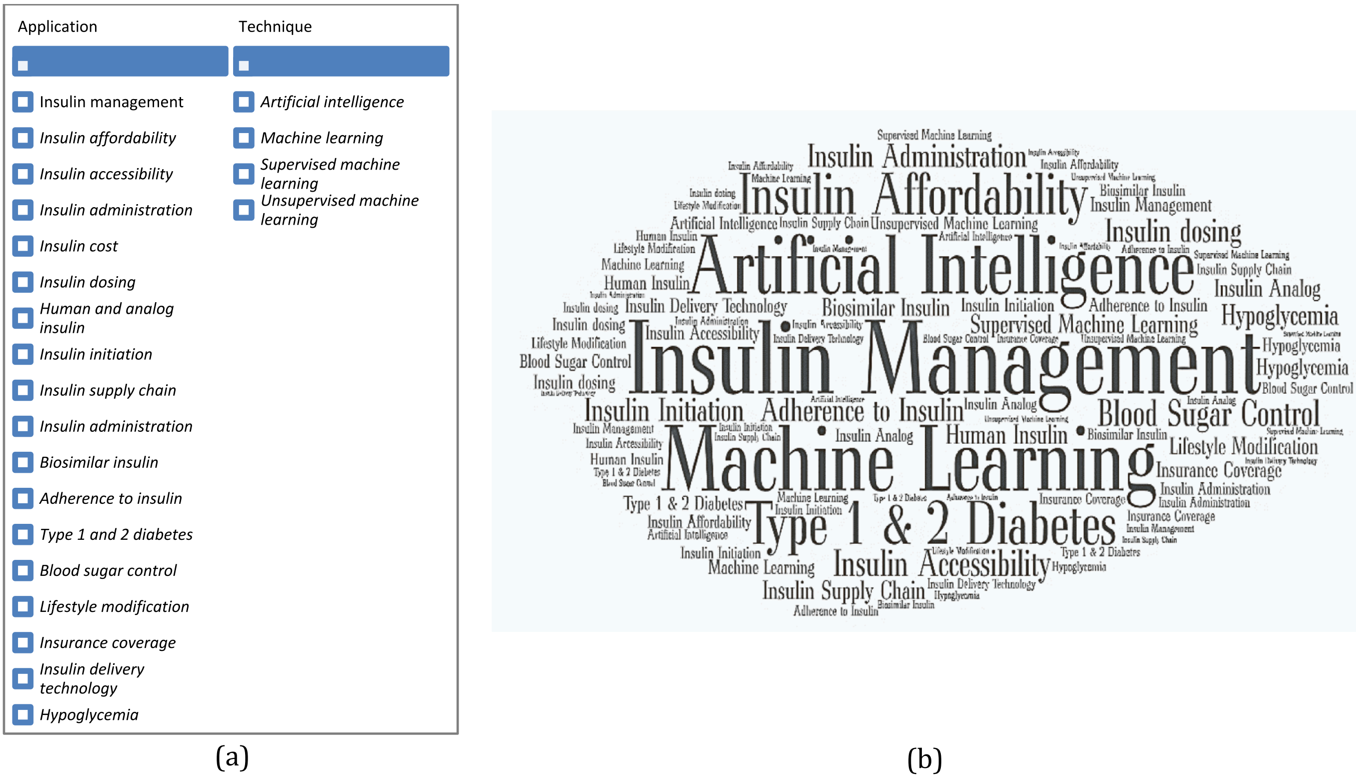


Fig. 2. List of keywords in (a) tabular format, and (b) cloud of words.

review that delves into various facets of insulin management. These encompass insulin dosage calculation, automatic insulin delivery, insulin administration, insulin injection policy, blood glucose prediction, initial insulin estimation, insulin resistance prediction, improving adherence to insulin treatment, predicting insulin related hypoglycemia risk, nocturnal hypoglycemia, impatient hypoglycemia, diabetes adverse complications prediction, and lifestyle-related diabetes management considering insulin treatment. Fig. 3 depicts the filtration process employed for the selection of papers in this study. Since this paper focuses on supervised ML, the readers can refer to Fox and Wiens [64], Tejedor et al. [65], Emerson et al. [66], Manzini et al. [67], Ahmad et al. [68], Yau et al. [69], and in order to reach papers in the application of unsupervised and instance-based ML in insulin treatment of diabetes patients.

3. Results

The management of insulin for diabetes can be classified into eight distinct categories, C1 to C8, as illustrated in Fig. 4. This section provides a comprehensive review of the implementation of ML models in each category. In Appendix A, Tables A2–A8 highlight the specific type of diabetes, the ML approach employed, the inputs and outputs utilized by each model, as well as the outcomes reported in each study. Moreover, Table A8 presents information about the data utilized for implementing and validating the proposed ML algorithms in each study.

3.1. *Insulin dosage calculation and response to it*

Mosquera-Lopez et al. [70] developed and evaluated a robust insulin delivery system, called the robust artificial pancreas that includes

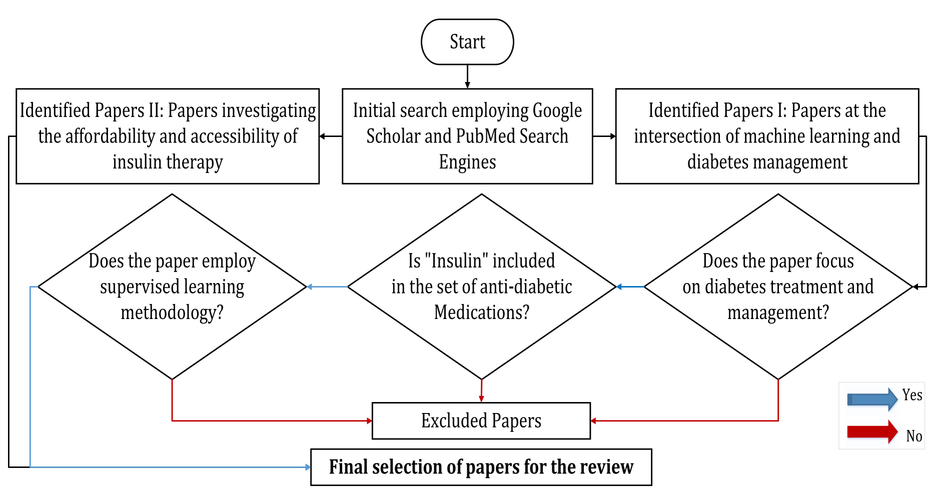


Fig. 3. Papers' filtration process.

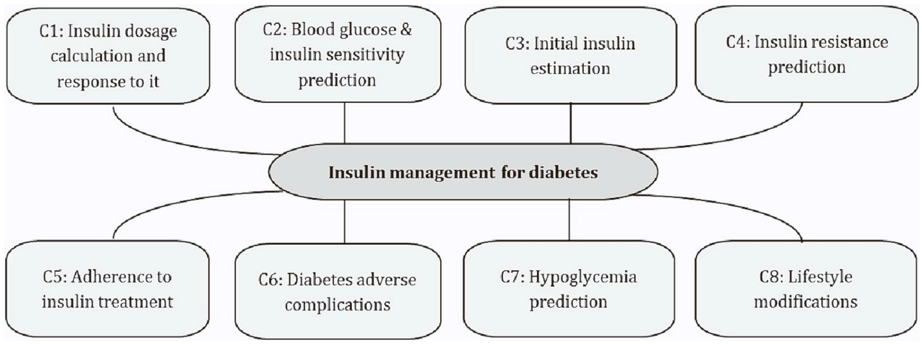


Fig. 4. Eight distinct categories of the literature in management of insulin for diabetes.

automated meal detection and carbohydrate content estimation using ML for meal insulin dosing. This system showed promising results in postprandial glucose control in a randomized, single-center crossover trial. Chen et al. [71] proposed an insulin dosage titration model using advanced ML methods, which has been implemented in the EHR workflow to form a clinical DSS of insulin dosage titration. The efficacy and safety of the proposed system has been preliminarily evaluated in T2D inpatients. Coales et al. [72] applied an ML approach to data from two randomized controlled trials characterizing individual mealtime insulin responses after subcutaneous injection of rapid-acting insulin in subjects with T1D treated by multiple daily injections. The study identified three distinct classes of patients based on their rapid-acting insulin responses, which were characterized by different pharmacokinetic summary statistics such as insulin area under the curve and insulin uptake. These classes were found to be associated with parameters of vascular health, such as blood pressure and arterial stiffness. Gupta and Jiwani [73] developed an ML model that uses a Recurrent Neural Network (RNN) with Long Short-Term Memory (LSTM) and ANN algorithm to predict a patient's insulin dose chart. de Farias and Bessa [74] developed an automated insulin delivery system using ANN. It can maintain normoglycemia without requiring meal announcements or carbohydrate calculations, and it is capable of handling inter- and intra patient variability.

The detection system of personalized insulin dose manipulation proposed by Levy-Loboda et al. [75], leveraged ML algorithms to analyze raw data generated using an insulin pump and it's paired CGM. The ML algorithms used in this study include decision tree, random forest (RF), support vector machine (SVM), K-nearest neighbor (KNN), and temporal probabilistic profiles (TPF) due their ability to handle missing values and leverage temporal abstractions. The main contribution of the proposed ML based model by Noaro et al. [170] was to improve the calculation of mealtime insulin boluses (MIB) in T1D therapy using CGM data. They developed four models based on multiple linear regression (MLR) and least absolute shrinkage and selection operator (LASSO) for MIB calculation using ML techniques in different mealtime scenarios. The models were compared with three state-of-the-art methods described in the literature which have the same objective. Jemima Jebaseeli et al. [76] proposed an Internet of Things (IoT) based Catboost ML algorithm suitable for efficiently handling the condition to predict the glucose level of the human body and suggesting the quantity of insulin required for the diabetic patient. Nguyen et al. [77] proposed an ML approach to estimate insulin requirements in hospitalized patients. The research aimed to ascertain if ML could provide a more precise forecast of the initial inpatient total daily insulin dose using EHR compared to the conventional dosing guidelines. Indragandhi et al. [78] proposed a bimodal insulin delivery system that utilizes IoT and ML techniques (linear regression, decision tree, and RF) to automate insulin drug delivery for comatose patients. This system aimed to replace existing insulin delivery systems that are costly and limited to certain hospitals, with a more affordable and accessible option. The proposed system also contained a rotor system controlled by a motor and can operate in either manual or automatic mode.

Noaro et al. [79,80] developed two nonlinear models including LASSO for IB estimation, RF, and Gradient Boosting Trees (GBT) for IB estimation in T1D therapy. They improved the limitations of the empirical standard formula commonly used for insulin injections, which can lead to critical hypo/hyperglycemic episodes. The nonlinear models took into account both blood glucose dynamics at mealtime and other relevant features, and were found to significantly enhance glycemic control over linear techniques in simulated frameworks. Peiró [81] compared different therapies for T1D treatment and to show that an artificial pancreas (AP) consisting of an insulin pump with CGM and hybrid "closed-loop" control algorithm trained with ML technology provides better glycemia control. Guzman Gómez et al. [82] developed models based on AI techniques, specifically SVM, for the estimation of basal insulin dose for T1D.

Due to deficiency of formulaic methods and closed-loop methods in blood glycemic control, Shifrin and Siegelmann [83] adopted a Markov decision process to model patient response to insulin treatment, enabling the system to dynamically adapt and discover a personalized insulin care policy that ensures stable blood glucose levels within desired ranges. To achieve even more precise glycemic control, they integrated an individualized health reward function into the model, which provides a tailored grading scheme for blood glucose levels, enhancing the accuracy of control. The model was solved using RL, resulting in an individualized and optimal insulin care policy capable of preventing hypoglycemia, minimizing the duration of high glucose levels and fluctuations, and adapting to changes in the patient's environment. Liu et al. [84] developed supervised ML methods such as SVM and RF classification to EHR data to build predictive models that can inform inpatient insulin management. The study found that individual blood glucose levels and insulin dosing are highly erratic and cannot be predicted precisely, but prescribing decisions can still be driven by the more reliable predictions of average daily glucose levels and whether any patient's glucose levels will be higher than the clinically desired range in the next day. Malmasi et al. [85] assessed the precision in detecting instances where patients documented a decline in insulin therapy using various methods, including sentence-level naïve Bayes, logistic regression, and SVM-based classification (both with and without SMOTE oversampling). Additionally, they explored token-level sequence labeling through conditional random fields (CRFs), as well as uni- and bi-directional RNN models featuring GRU and LSTM cells. Rule-based detection using the Canary platform was also employed in the evaluation process. Daskalaki et al. [86] presented a novel control scheme for AP that addresses the challenges of inter−/intra-patient variability and personalization of insulin treatment. The control scheme was based on a real-time adaptive algorithm that optimizes insulin infusion for personalized glucose regulation.

3.2. Blood glucose and insulin sensitivity prediction

Kurdi et al. [87] used supervised ML algorithms including multivariable logistic regression, RF, and KNN to predict self-care behaviors and glycemic control in T1D patients on insulin pump therapy. The features were used to predict the likelihood of patients meeting self-care criteria and achieving good glycemic control within six months. Zafar et al. [88] assessed different ML-based prediction methods including KNN, RF, LSTM, SVM, and Gradient Boost (XGBoost) for glucose forecasting in insulin delivery systems, with a focus on their limitations and performance in terms of accuracy and resource consumption. Annuzzi et al. [89] investigated the impact of nutritional factors, including carbohydrates, proteins, lipids, fibers, and energy intake, on predicting blood glucose levels in the short and middle term using ML methods. Annuzzi et al. [90] studied the he impact of specific input features (preprandial blood glucose values, insulin dosage, and various mealrelated nutritional factors such as intake of energy, carbohydrates, proteins, lipids, fatty acids, fibers, glycemic index, and glycemic load) on blood glucose levels prediction by employing explainable artificial intelligence methodologies.

Tarumi et al. [91] examined three methods for leveraging EHR data across various healthcare systems to predict the outcomes of pharmacotherapy for T2D including long-acting insulin medication class. Among these approaches, selecting better and weighted average preserved data within institutional confines by utilizing pre-existing prediction models. In contrast, the third approach, known as combining data, involved consolidating raw patient data into a unified dataset.

Szabó et al. [92] evaluated the clinical performance of two different AI-based methods for predicting insulin sensitivity in tight glycemic control treatment in intensive care settings. The performance of these methods was compared with the clinically validated intensive control insulin-nutrition-glucose model, which is widely used in tight glycemic control treatment. Miller et al. [93] developed a hybrid statistical and physiological model of insulin-glucose dynamics for producing long-term forecasts from real-world T1D management CGM, insulin, and meal log data. The hybrid model combined a T1D simulator with a ML sequence model. Specifically, the ML component of the model consisted of a state-space model and a neural network. The state-space model captured the underlying physiological dynamics of insulin-glucose interactions, while the neural network component learned to map from past observations to future glucose levels. The neural network was trained using maximum-likelihood estimation to fit the parameters that produce good forecasts. However, due to the non-linearity introduced by the T1D simulator, computing the marginal likelihood of the data was not possible in closed form, which complicates inference. Nonetheless, this hybrid approach improved forecasts over purely mechanistic or purely statistical approaches on real-world T1D data and produces physiologically plausible counterfactual predictions under alternative insulin and meal schedules. Wang et al. [94] examined the overall condition of blood glucose regulation in insulin treated T2D patients receiving outpatient care in northern China. Additionally, the study investigated the potential utility of combining an elastic network (EN) with ML algorithms to predict diabetic blood glucose control. Xie and Wang [95] compared the performance of several commonly known ML models versus a classic Autoregression with Exogenous inputs (ARX) model in the prediction of blood glucose levels using time-series data of individuals with T1D who were under insulin pump therapy. The ML algorithms used in this study include ML-based regression models and DL models such as a vanilla LSTM network and a Temporal Convolution Network (TCN). The ML-based regression models implemented in this study include SVM, RF Regression, Gradient Boosting Regression (GBR), and Multi-Layer Perceptron Regression (MLPR). These algorithms were compared to the classic ARX model.

Benyó et al. [96] applied deep neural network (DNN) based methods for patient state prediction and insulin sensitivity prediction for personalized glycemic control in intensive care. Ngufor et al. [97] developed a mixed-effect ML framework that effectively utilizes temporal heterogeneous, sparse and varying-length patient characteristics inherent in longitudinal data that can help predict longitudinal alteration in glycemic control measured by hemoglobin A1c (HbA1c) among well-controlled adults with T2D with high accuracy, sensitivity, and specificity. Rodríguez-Rodríguez et al. [98] utilized the big data and ML techniques including Autoregressive integrated moving average (ARIMA), RF, and SVM in predicting short-term blood glucose levels in T1D.

3.3. Initial insulin estimation

Musacchio et al. [99] used transparent ML (i.e. Logic Learning Machine (LLM), a type of explainable AI) to identify the key drivers behind the decision to start insulin therapy in individuals with T2D. The study found that the most important factors were high HbA1c levels, long disease duration, and a history of cardiovascular disease. The results showed that the LLM algorithm was able to accurately predict insulin initiation, which is comparable to other state-of-the-art ML algorithms. Hankosky et al. [100] identified the predictors of insulin pump initiation among individuals with T2D using ML. The study used a US claims database to analyze the factors associated with insulin pump initiation among T2D patients (significant predictors: age, gender, comorbidities, and medication use). Fujihara et al. [101] aimed to assess the predictive capabilities of ML models in determining when specialists would initiate insulin treatment for T2D patients. The Japan Diabetes Clinical Data Management (JDDM) Study Group, composed of diabetes specialists, was used for evaluation. The researchers compared the decisions made by the ML models, trained on the database of specialists' judgments, with those made by no specialists during the first consultation.

3.4. Insulin resistance prediction

Leal-Witt et al. [102] used an ML model (XGBoost algorithm using of a k-fold cross-validation approach to partition the dataset into training and test sets) to reveal an association between phenylalanine concentrations in dried blood spots and the risk of developing insulin resistance (IR) in adult subjects with phenylketonuria. According to Saxena et al. [103], although IR is a crucial factor in the development of T2D and metabolic syndrome, the specific pathways connecting these two are not well understood. To identify shared genes, LASSO feature selection method was utilized to identify metagenes that play a primary role in the transition from IR to T2D. They trained LASSO, SVM, XGBoost, RF, and ANN ML models on the expression profiles of these genes, with the ANN performing the best. Zhang and Wan [104] developed logistic regression, SVM, XGBoost, RF, and CatBoost ML models to predict IR in children aged 6–12 years using ML allowing for early intervention and prevention for identified children at risk for developing diabetes and cardiovascular disease. Lee et al. [105] focused on chronic kidney disease and its association with IR, which worsens renal and patient outcomes considering both macronutrients and micronutrients. They employed various ML algorithms, including RF, XGboost, logistic regression, and DNN, to predict IR using the measure homeostasis model assessment of IR (HOMA-IR). Receiver operating characteristic (ROC) curves were compared among the different algorithms, and SHAP values were utilized to explain the functioning of the ML models. Ultimately, the RF algorithm exhibited the highest area under the ROC curve (AUC) and the most significant differentiation in SHAP values.

Park et al. [106] predicted IR using an ML algorithm. The study was conducted on a population-based cohort in Korea, and the results showed that the poly-genetic variants belonged to the 15-feature prediction model when environmental factors, including nutrient intake and lifestyles, were not included. The study also found that pulse and seasons with other medical health-checkup were included in the 9-feature model, which can be easily implicated into the smart watch to check IR and provide a health-related personal warning daily. Kang et al.

[107] presented an ML-derived gut microbiome signature that predicts fatty liver disease in the presence of IR. The authors developed an RF classifier using fecal 16S rDNA sequencing data from a cohort of 777 individuals and evaluated its performance using metrics such as accuracy, AUC, kappa, and F1-score. The classifier performed better in individuals with IR and was further optimized using genetic algorithm.

Abdesselam et al. [108] proposed an ML approach to estimate the HOMA-IR cut-off value for identifying individuals at risk of IR in a given ethnic group. They used cluster analysis and ML techniques such as the k-means clustering algorithm and a self-organizing map (SOM) clustering algorithm to group individuals based on their HOMA-IR values and other clinical parameters such as age, gender, and body mass index (BMI) to identify the optimal cut-off value for an Omani Arab population living in Nizwa. Qazmooz et al. [109] used ML algorithms to identify immune, trace element, and opioid biomarkers that can predict atherogenicity and IR indices. The study provides a comprehensive analysis of these biomarkers in individuals with unstable angina, which can help in the early diagnosis and treatment of cardiovascular disease. Chakradar et al. [110] proposed non-invasive approach to identify IR using ML techniques. This approach used triglycerides and HDL-c ratio, along with 18 other parameters, to identify IR without the need for invasive clinical processes and was validated with a stratified cross-validation test and compared with the state-of-art algorithms. Aggarwal [111] proposed a joint strategy of ML and DL for identifying IR using non-invasive techniques. A novel method for diagnosing HOMA-IR was introduced by Hall et al. [112], which utilized ML techniques applied to the physical characteristics of patients. By analyzing anthropometric patient features, a predictive model was created that can accurately diagnose IR.

3.5. Adherence to insulin treatment

Thyde et al. [113] explored how ML based on CGM data can be used to detect missed once-daily basal insulin injections in T2D patients. They evaluated various ML models to identify adherence and explored the potential enhancement of performance by combining features derived from both expert knowledge and automated learning. The results showed that the DL methods (neural networks) outperform the simple feature-engineered models for detecting missed insulin injections and combining expert-dependent and automatically learned features can further improve performance.

3.6. Hypoglycemia prediction

Parcerisas et al. [114] proposed a DSS that utilizes ML algorithms to predict and prevent nocturnal hypoglycemia in T1D patients who are undergoing multiple dose insulin therapy. The study used various data sources, optimization metrics, and mitigation measures to design population and personalized models that can be used to improve confidence toward self-management of the disease. The personalized models showed better performance than population models, indicating that individualized approaches to diabetes management may be more effective. Dave et al. [115] proposed a feature-based ML model for real-time hypoglycemia prediction in T1D patients. Mueller et al. [116] applied ML models to identify predictors of hypoglycemia and other clinical and economic outcomes among treated people with T2D using structured data from a large, geographically diverse administrative claims database.

Elhadd et al. [117] utilized ML techniques to predict metabolic outcomes in individuals with T2D who fast during Ramadan. Bosnyak et al. [118] developed a predictive model for hypoglycemia risk in patients T2D using basal insulin treatments. The study utilized advanced analytical methods, including ML, to analyze EHR data and identify potential subgroups of patients who are at lower risk of hypoglycemia when treated with basal insulin compared with another and predict hypoglycemia-related cost savings in these subgroups. Seo et al. [119] developed and evaluated an easy-to-use, computationally efficient ML algorithm to predict postprandial hypoglycemia using unique data-driven features derived from the data.

Oviedo et al. [120] proposed an insulin hypoglycemia reduction system based on postprandial hypoglycemia predictions using ML techniques. This system aims to improve glycemic control in subjects with T1D who use multiple insulin injections and monitor their capillary glucose levels. They used several ML algorithms to predict postprandial hypoglycemia. The system generates a bolus reduction suggestion as the scaled weighted sum of the predictions.

3.7. Distribution and trends of reviewed works across the categories

After reviewing the papers in the survey, the preparation of Fig. 5a–e to display the distribution and trends of the reviewed works across the aforementioned categories is undertaken.

According to Fig. 5a, the results indicate that 16 % of the reviewed works concentrate on C1, which entails insulin dosage calculation and the corresponding response. Additionally, 12 % of the papers revolve around C4, which pertains to the prediction of insulin resistance. Furthermore, 10 % of the reviewed works fall under the scope of C2, involving predictions related to blood glucose levels and insulin sensitivity. Finally, 9 % of the papers focus on C7, which encompasses the prediction of hypoglycemia. Fig. 5b provides insights into the focus of studies on each type of diabetes and their relationship to the eight aspects of insulin management. The analysis reveals the distribution of research across the various categories and sheds light on the prominence of specific diabetes types in each aspect. Fig. 5c–e present an analysis of the ML algorithms employed in the respective categories of C1, C2, and C7. In the domain of C1, which focuses on insulin dosage calculation and response, the most utilized ML models are RF and neural networks. Moving on to C2, which involves blood glucose and insulin sensitivity prediction, RF and SVM emerge as the predominant ML models. Similarly, RF and SVM are the top ML models employed in C7, which deals with hypoglycemia prediction. Tables A1 to A5 in the Appendix section are presented to illustrate both the clinical challenges and their corresponding technical solutions derived from the diverse array of studies discussed. These tables offer a structured overview of the healthcare issues addressed in the respective research, alongside the innovative technical approaches employed to tackle them.

Based on the findings and the detailed information presented in Tables A2–A8 in the Appendix, which outline the specific inputs of the models, it is evident that studies employing ML in various facets of insulin management often overlook cost-related factors and fail to address aspects reflecting insulin affordability or accessibility. The subsequent section delves into a thorough examination of the limitations associated with these studies, exploring different clinical aspects related to insulin affordability and accessibility. Additionally, the subsequent highlights potential research opportunities in this domain.

4. Discussion: limitations and research opportunities

With regard to market dynamics and research opportunities, the global insulin market is anticipated to experience steady growth due to factors like increasing diabetes prevalence and advancements in technologies such as ML and AI. ML applications in insulin management encompass continuous glucose monitoring data analysis, insulin dosing optimization, and predictive analytics for complications. These applications leverage various ML techniques to enhance glucose control and personalize treatment strategies for individuals with diabetes. ML-driven innovations in insulin management, like closed-loop systems, present significant market potential. Research endeavors in this domain are concentrated on refining glucose control, minimizing hypoglycemia, and averting long-term complications, with ML serving a pivotal role in predictive modeling and treatment refinement. It's crucial to address integration with healthcare systems and comply with regulatory

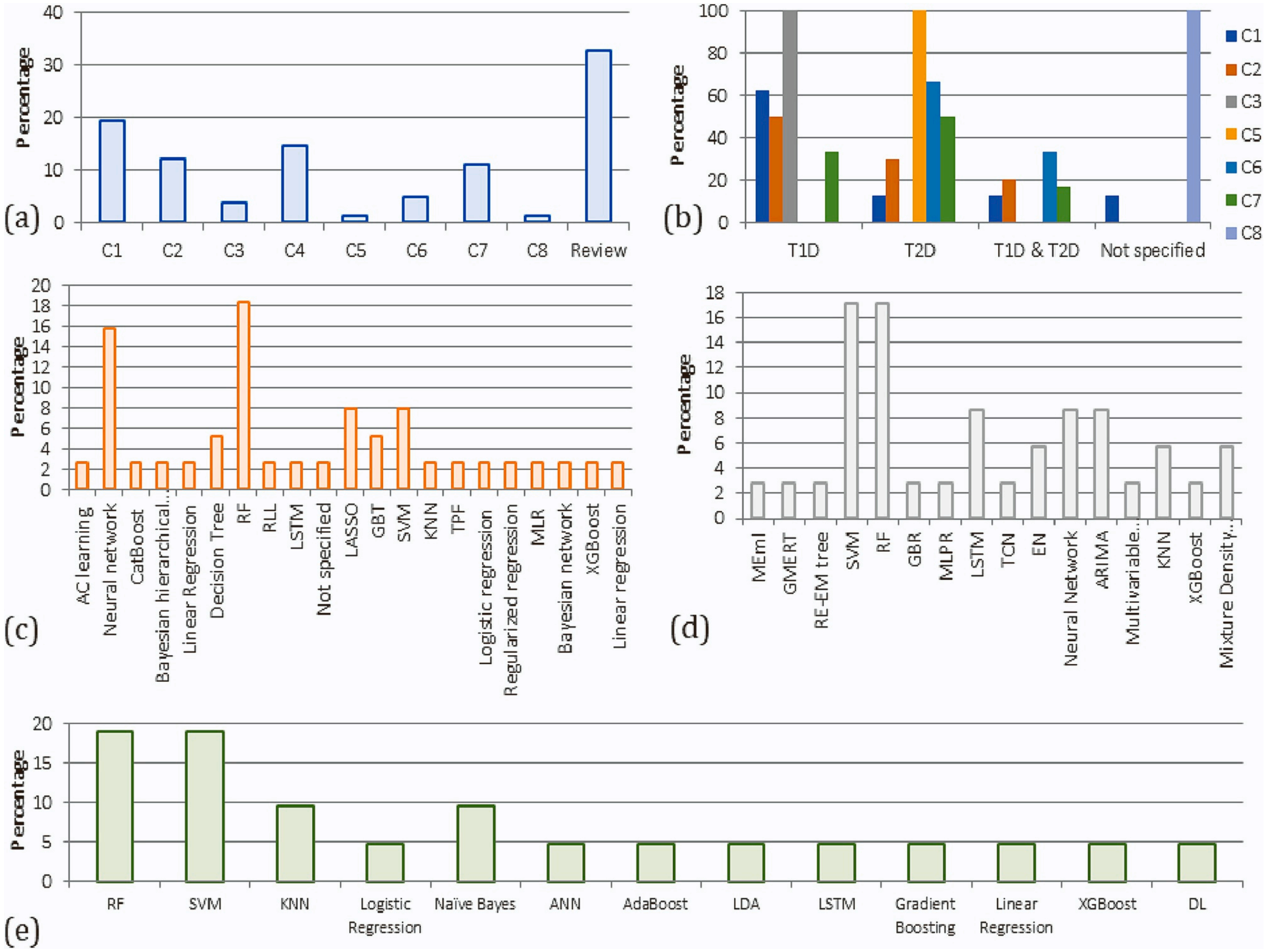


Fig. 5. The distribution of the reviewed papers in terms of: (a) the introduced categories, (b) Diabetes' type, (c) most common ML algorithms in C1, (d) most common ML algorithms in C2, and (e) most common ML algorithms in C7.

standards for successful market penetration. Overall, the intersection of ML technology and insulin management holds promising prospects for innovation, market expansion, and enhanced patient outcomes in diabetes care. Although continuous research, collaboration, and investment efforts will be instrumental in propelling forward the field of insulin therapy and diabetes management, the limitations of the existing research should be recognized. In this section, the limitations of studies that may have been impactful on the results or contributed to a gap between the research and reality are presented. Furthermore, research opportunities are discussed for further investigation into the application of ML models in order to improve the affordable and effective management of insulin for diabetes.

4.1. Limitations

In the rapidly advancing field of ML applications in insulin management for diabetes care, it is essential to critically evaluate the limitations that may impact the real-world effectiveness and broader adoption. These limitations can be broadly categorized into distinct areas, including data-related challenges, modifiable factors such as data-related, algorithm design and validation, modifiable factors (insulin type, dose, timing, etc.), subject preferences, habits, and therapeutic education (meals, physical activity, etc.), and sensor and technology limitations. Table 1 is provided to present more details about each limitation categories in reviewed papers. Understanding and addressing these limitations is crucial for the development and deployment of effective ML-based insulin management systems.

Table 1
Limitations of insulin management.

Study	Limitations				
	Data	Algorithm design & validation	Modifiable factors	Subject preferences, habits, & therapeutic education	Sensor & technology
[58]	x	x			
[79,80]	x				
[77]	x				
[63]	x				
[53]		x			
[57]		x			
[117]		x			
[121]			x		x
[122]			x		
[82]			x		
[123]				x	
[124]				x	
[70]				x	
[125]					x

Data related limitations have been tracked down to having limited supporting data for building accurate algorithms, errors in patient behavior, carbohydrates miscalculations, and sensor readings, erroneous, missing, and unavailable data in electronic health record data (impacting the reliability and completeness of the dataset), and its need for huge case studies, which could include non-relevant information. The algorithm design and validation limitation incudes validation of models using retrospective data sets, lack of prospective validation of technical advances, lack of generalizability in validation techniques. Lack of validation in realistic free-living conditions, validation of models in simulated environments, small sample sizes in studies, and over-reliance on in silico evaluations. Limitations of modifiable factors entails regular data uploads, potentially disrupting routine clinic visits, participant confirmation in meal detection, potentially affecting user experience, uncertainty and noise in real-world scenarios, influencing blood glucose levels and degrading control algorithms, and challenges in the practical clinical application due to variations in variables across patient populations. The limitations caused by subject preferences, habits, and therapeutic education comprise of inability to model physical activity, stress, temporal insulin sensitivity factors, and time-based carbohydrate-to-insulin ratios, challenges in dealing with interaday variability due to temporary events, and dependence on participant confirmation for meal detection. And sensor and technology limitations are caused by frequent uploading and downloading of data for insulin titrations, data sharing and subsequent dose adjustments through online or mobile applications, the relatively high cost of CGMs limiting wider adoption among diabetic patients, and participant confirmation required for meal detection, impacting data accuracy.

Finally, to date, there have been no studies in the literature that specifically employ ML techniques to facilitate recommendations by prominent institutions and working groups in order to address the issue of high insulin costs, improve affordability, and enhance accessibility and provide insights into the economic factors influencing the insulin management field of study.

4.2. *Research opportunities*

According to Nature biotechnology (2022) up to 25 % of patients in the US are currently rationing their insulin intake, which puts them at significant risk of potentially life-threatening complications, the importance of affordable access to insulin cannot be overstated. Moreover, the absence of similar alternatives for glucose management, such as dietary modifications, weight loss, exercise, and oral anti hyperglycemic medications available to those with T2D, exacerbates the situation for people with T1D [15]. Fig. 6 provides a schematic representation of the barriers to insulin access.

This section aims to concentrate on the utilization of ML models to enhance the accessible and affordable effective insulin treatment, in accordance with the recommendations provided by the Endocrine Society [127,128] and the insulin access and affordability working group [10]. Hence, the future research opportunities are categorized into the following:

4.2.1. *Insurance coverage type*

4.2.1.1. Clinical aspect. The categorization of patients dependent on insulin based on their insurance type plays a vital role in understanding how their healthcare coverage influences their access to insulin and related supplies [10]. The cost and availability of insulin are significantly impacted by insurance coverage, which is a critical aspect of diabetes management. Here are some common insurance categories that can affect patients dependent on insulin [129]: Medicare (insurance program for people 65 or older, Insulin covered under Medicare Part D, Insulin covered under Medicare Part B, Insulin out-of-pocket (OOP) cost-sharing), Medicaid, private/commercial insurance (State regulated health insurance plans, Other private insurance coverage), Uninsured. Healthcare costs associated with diabetes are significant, especially when it comes to OOP expenses for insulin and patients experience varying financial responsibilities based on the type of insurance plan they have [4]. As it is demonstrated in Fig. 7, patients who are uninsured and those with private insurance face substantial costs in obtaining insulin [130].

Additionally, Fig. 8 presents a comparative distribution of individuals within different healthcare coverage categories in the US based on their usage of insulin, categorized as “Insulin users” and “Non-Insulin users” [130]. The data is segmented across four coverage types: Medicaid, Medicare, Private, and uninsured. Fig. 9 displays the distribution of insulin prescription acquisitions based on coverage type, taking into account instances of personal expenditure [13]. On the whole, 63 % of insulin acquisitions involved some form of cost-sharing. Among these, 32 % of acquisitions necessitated payments surpassing $35, while

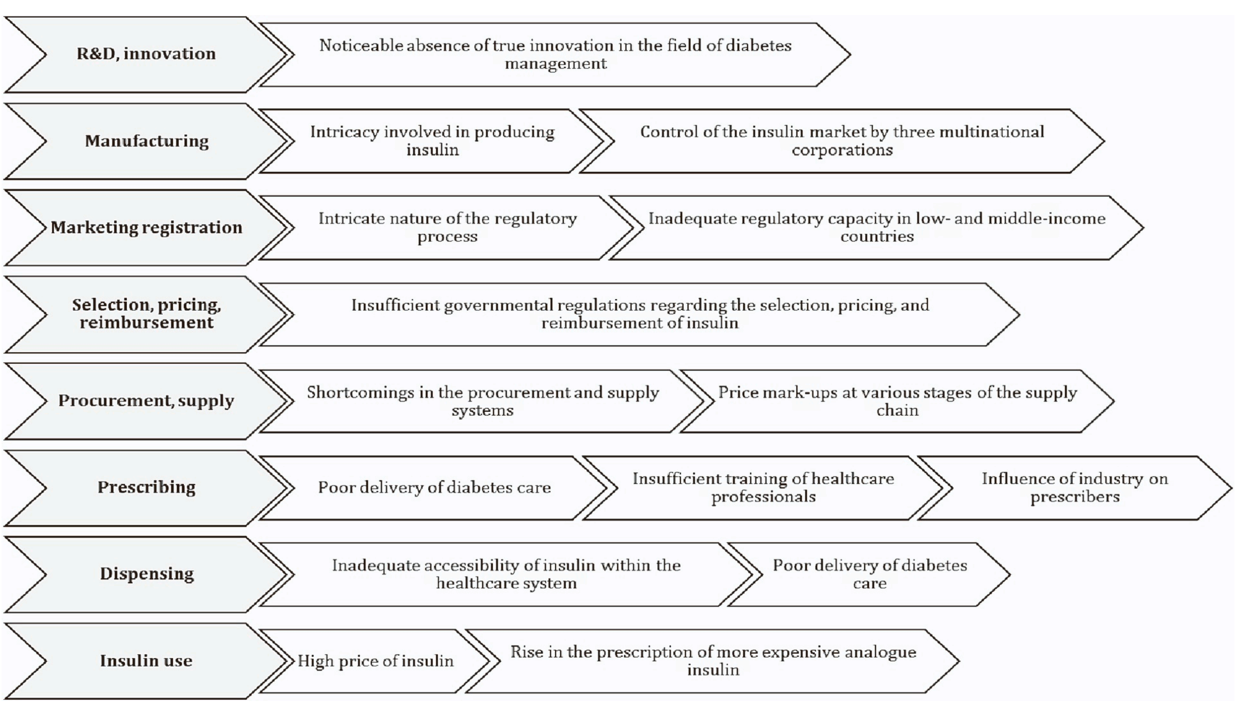


Fig. 6. Barriers to insulin access encountered at each stage of the WHO’s insulin life cycle framework [11,19,126].

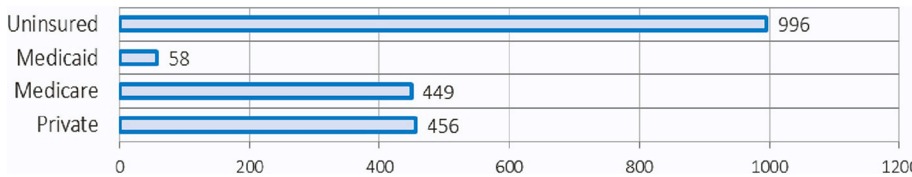
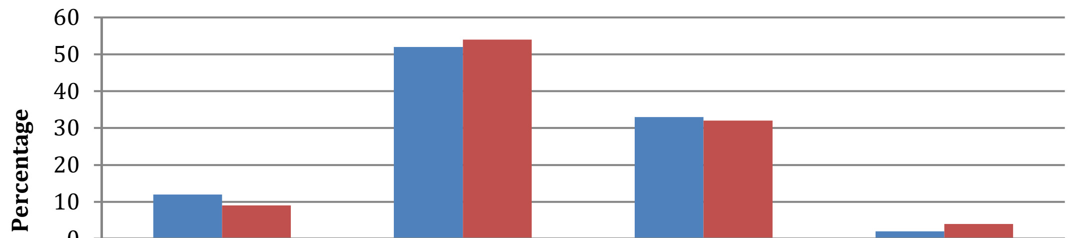


Fig. 7. Average annual OOP costs for insulin in 2019 [130].



	Medicaid	Medicare	Private	uninsured
Insulin users	12	52	33	2
Non-Insulin users	9	54	32	4

Fig. 8. Distribution of individuals as insulin and non-insulin users across different healthcare coverage categories [130].

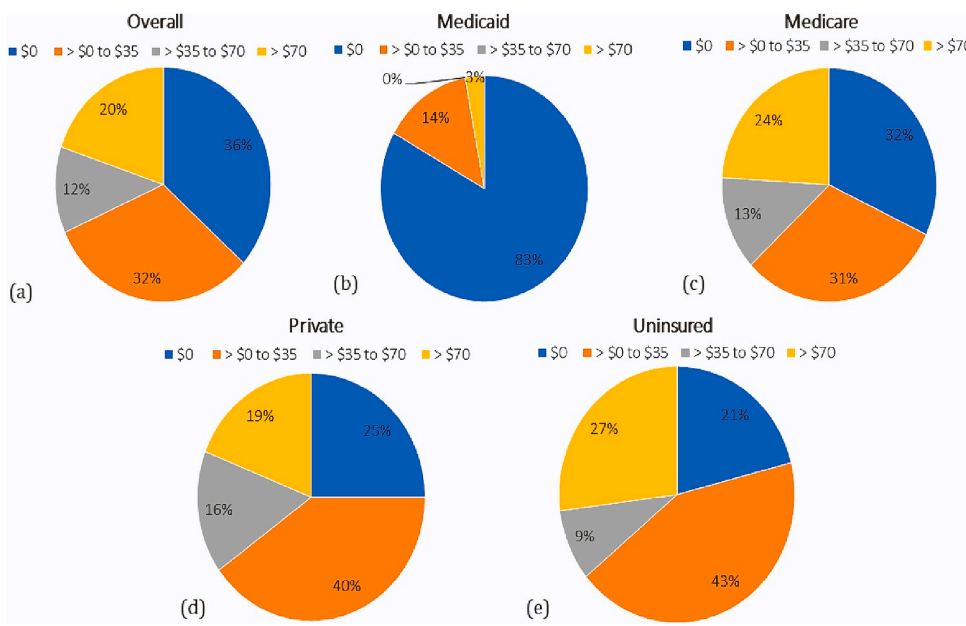


Fig. 9. Share of insulin prescription fills with cost sharing per fill in 2019, (a) overall, (b) Medicaid, (c) Medicaid, (d) private, and (e) uninsured [13].

20 % demanded payments exceeding $70. Notably, patients covered by private insurance and those without insurance were notably more prone to encountering cost-sharing requirements compared to other coverage categories. In contrast, a majority of Medicaid beneficiaries acquiring insulin prescriptions faced no cost-sharing obligations. For Medicare patients, 68.5 % experienced out-of-pocket expenses, with 37 % of them incurring costs beyond $35 per prescription fill – an inclusive figure that encompasses nearly a quarter of individuals who paid over $70 per acquisition. Underinsured individuals may encounter higher OOP costs in the form of prescription co-pays, co-insurance, or deductibles [15]. In contrast, uninsured individuals are solely responsible for bearing the entire cost of their insulin [131]. The Inflation Reduction Act limits insulin OOP costs for Medicare Part D and Part B plans to $35 per month and also reduces overall OOP drug spending within Medicare [12,13].

4.2.1.2. Technical aspect. There is insufficient research on leveraging insurance variables to enhance ML models' accuracy and effectiveness in improving insulin affordability. Research explores integrating insurance data into ML algorithms for cost prediction, treatment outcome analysis, risk assessment, and personalized interventions.

4.2.2. Insulin type selection

4.2.2.1. Clinical aspect. Insulin analogs have emerged as the dominant players in the insulin market, causing some older human insulin products to be phased out [132,133]. According to the Endocrine Society [127,128] guidelines, the most cost-effective insulin option that aligns with the patient's specific clinical requirements should be prescribed.

For individuals with T2D, managing their condition efficiently is achievable with the use of lower-priced human insulin such as NPH and regular insulin [127,128,132,134,135]. While human insulin continues to be a viable alternative for those with T1D, insulin analogs are generally considered the preferred treatment for this patient group [133]. An investigation has shown that a preference for expensive insulin is more common among higher-ranking physicians and trainees may adopt these practices from their senior colleagues [136]. Transitioning from insulin analogs to human insulin dosage for patients who are suitable candidates relies heavily on expert knowledge [135,137]. Considering the increasing scarcity of proficient medical practitioners capable of adjusting human insulin dosages, the present clinical approach falls short in its capacity to deliver the necessary fine-tuning of human insulin levels for enhancing diabetes management [127,128,136].

4.2.2.2. Technical aspect. Thus, ML models can facilitate insulin type selection and developing human insulin dosage titration system. These models can enhance the comfort of use for insulin selection, which is a crucial factor influencing a physician's choice when prescribing affordable insulin [134,136,138]. The study conducted by Mangu and Nyayapati [139] is the only known research that partially relates to this area. Their study investigates customer satisfaction for insulin brands in the Indian market, specifically focusing on service levels and response time. They utilize unsupervised ML algorithms and Principal Component Analysis (PCA) to identify three significant components influencing customer satisfaction: Interaction factor, Personal touch factor, and Swiftness factor.

4.2.3. Biosimilar insulin and market competition

4.2.3.1. Clinical aspect. The introduction of biosimilar insulin and the establishment of interchangeable insulin options play a vital role in breaking the barriers of a closed market lacking competition [140]. This development is crucial for reducing insulin costs and improving its overall affordability [26,127,128,141–145]. According to the ASPE [130], the principal advisor to the Secretary of the US Department of Health and Human Services (HHS) on policy development, the extent of these potential cost savings relies on the establishment of a competitive landscape for each insulin product, which encompasses factors such as the speed and number of biosimilar competitors entering the market for each insulin type.

4.2.3.2. Technical aspect. The exploration of utilizing ML models to predict market competition arising from biosimilar insulins and magnitude of future saving, short and long-term cost benefits, and substitution allowances represents a crucial avenue for future research and present significant implications for policymakers, potentially prompting them to consider adjusting the approval process for biosimilar insulin products [130,146].

4.2.4. Mental health issues

The issue of insulin insecurity, characterized by significant disruptions in access, has brought forth another serious concern: psychological distress [15,147]. This potential development of mental health conditions, such as loss of sleep, high levels of anxiety and stress, depression and even post-traumatic stress disorder (PTSD) can cause blood glucose levels fluctuations [15,147].

4.2.4.1. Technical aspect. In addressing this complex issue ML can serve as a powerful computational tool to enhance our understanding of the emotional and behavioral aspects of PTSD. By analyzing large datasets of patient information, ML models can learn general rules and patterns, aiding in the development of accurate diagnostic classification models for identifying individuals with PTSD resulting from the high cost of insulin, insulin rationing, and the financial hardships associated with obtaining insulin for diabetes patients.

4.2.5. Insulin delivery selection

4.2.5.1. Clinical aspect. To choose the appropriate type of insulin and administer it correctly, it is important to have knowledge about the onset and duration of its effects, the timing of doses, and the method of delivery [148,149]. The effectiveness and safety of insulin therapy have been enhanced by advancements in insulin delivery and blood glucose monitoring technologies [150]. These advancements include the transition from vials and glass syringes to insulin pens and pumps, as well as the shift from traditional self-monitoring of blood glucose with lancets and test strips to CGM systems, real-time CGM systems, and flash glucose monitoring systems [150]. In September 2016, the FDA granted approval for AP systems, which enable automated adjustments of basal insulin infusion rates and/or bolus corrections based on CGM readings similar to physiological insulin delivery [150]. These devices contribute to the enhancement of glucose control, the reduction of glucose variability, and the occurrence of hypoglycemia less frequently [23,151,152]. To guarantee affordability, it is crucial to take into account all the necessary components of insulin therapy [4,148,153].

4.2.5.2. Technical aspect. Conducting future research to match patients with different insurance coverage to the appropriate delivery system would be a valuable endeavor [23,154]. By analyzing large datasets and using ML algorithms, patterns and correlations between insurance coverage and the most cost-effective insulin delivery systems for different patient profiles can be identified.

4.2.6. Cost-related suboptimal insulin use and adherence

4.2.6.1. Clinical aspect. Insulin's increasing financial pressures and barriers have led to the emergence of risky compensatory behaviors (such as rationing), personal or financial sacrifices, and the adoption of unconventional approaches (like trading) [155]. Insufficient access to appropriate healthcare, insufficient awareness of the repercussions of noncompliance, and financial constraints are the main factors leading to rationing of insulin among diabetes patients [156,157]. The following questions can be used to gauge cost-related insulin underuse [158]: (1) Did you consume less insulin than prescribed? (2) Did you attempt to stretch out your insulin supply? (3) Did you take smaller doses of insulin than prescribed? (4) Did you discontinue the use of insulin? (5) Did you not fill an insulin prescription? (6) Did you not initiate insulin treatment? The high OOP costs and cost sharing associated with insulin lead to individuals sacrificing other essential needs, engaging in rationing behaviors by taking less than the prescribed amounts of insulin, creating barriers to prescription satisfaction, adherence, and affordability [130,149,152,159,160].

4.2.6.2. Technical aspect. First research topic is utilizing ML techniques to analyze healthcare data, patient demographics (especially income and insurance coverage), and socioeconomic factors to identify patterns and predict the prevalence of cost-related insulin underuse and catastrophic spending among diabetes patients in primary care settings [161]. The goal would be to provide healthcare providers with early identification of patients at risk of cost-related insulin underuse, enabling targeted interventions and support to mitigate the impact of financial barriers on insulin therapy adherence. On the other hand, Insulin affordability is closely linked to adequate housing and food security, prioritized by federal agencies like HHS and US Department of Agriculture (USDA). Housing instability and challenges in paying utilities can compromise the quality of insulin due to the need for refrigerated storage. Additionally, food insecurity, which hampers access to consistent and appropriate dietary intake, poses health risks for individuals on insulin regimens [130,162]. Therefore, another research topic is exploring the relationship between housing and food insecurity and their impact on insulin affordability and management. The aim of the proposed model is to develop predictive models that analyze data on housing instability, utilities payment challenges, and food insecurity to identify individuals at higher risk of compromised insulin quality and suboptimal dietary adherence.

4.2.7. Patient cost-sharing program selection

4.2.7.1. Clinical aspect. Multiple initiatives are underway to alleviate the impact of high OOP spending. These include the Inflation Reduction Act [130], the involvement of insurers, Pharmacy Benefit Managers (PBMs), and manufactures [130] by offering pre deductible coverage where patients receive coverage at no cost [152], patient assistance programs [127,128,130], drug discount programs (copay cards, savings programs) [163], and the availability of pricing databases like goodrx.com, blinkhealth.com, and costplusdrugs.com [8]. Fig. 10 illustrates the variety of alternatives and their eligibility of manufacturer-sponsored programs aimed at reducing insulin cost sharing.

However, the effectiveness of patient assistance programs in enhancing insulin accessibility remains uncertain, as there are concerns regarding the lack of transparency in eligibility requirements, complicated application and renewal processes, and potential limitations to specific brands and treatments [127,128]. These requirements differ among companies, and the annual application process can pose challenges as patient assistance programs can be complex to navigate [127,128]. Moreover, there are concerns about the underutilization of patient access programs provided by the three major insulin manufacturers in the US [164].

4.2.7.2. Technical aspect. Thus, ML techniques can be developed as a model that maps patients to their most suitable cost sharing program, considering eligibility requirements, application processes, brand limitations, and treatment preferences. By analyzing data on patient characteristics, medical history, and financial factors, the model will provide personalized recommendations, improving transparency, accessibility, and utilization of patient assistance programs.

5. Conclusion

This comprehensive review explores the potential of ML in insulin management, covering various aspects targeted solutions for managing diabetes, encompassing early detection, predictive analytics, personalized treatment plans, continuous glucose monitoring, optimized insulin dosing, behavioral coaching, remote monitoring, telemedicine, and risk assessment for complications. Implementing ML in these domains enables healthcare providers to enhance patient outcomes and alleviate the impact of diabetes on individuals and healthcare systems, leading to improved outcomes and cost-effective approaches. However, it is crucial to acknowledge the limitations of the existing literature and address the research gaps to advance the field further. In the future, AI and ML are expected to revolutionize diabetes management with personalized medicine, predictive analytics, advanced closed-loop systems, remote monitoring, healthcare automation, improved diagnostics, behavioral support, as well as insurance coverage, selection of insulin types, biosimilar insulin utilization, mental health considerations, and patient cost-sharing programs. Additionally, optimizing insulin delivery options and addressing suboptimal insulin use and adherence can contribute to more accessible and affordable insulin management practices. By envisioning an improved and cost-effective insulin management system, this review aims to pave the way for transformative solutions in diabetes care. Embracing the potential of ML and incorporating it into clinical practice can revolutionize insulin management, ensuring that patients have access to the life-saving treatment they require while mitigating the financial burdens associated with it.

CRediT authorship contribution statement

Maryam Eghbali-Zarch: Writing – original draft, Visualization, Validation, Investigation, Conceptualization. **Sara Masoud:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Table A1
Review papers on the application of AI and ML in diabetes management.

Study	Provided overview	Categorizing point
Afsaneh et al. [39]	Applications of ML and deep learning (DL) models in the prediction, diagnosis, and management of diabetes	Prediction, diagnosis, and management of diabetes
Chaki et al. [40]	Techniques and advancements in the field of diabetes detection, diagnosis, and self-management using ML and AI	Prediction, diagnosis, and management of diabetes
Nomura et al. [37]	Potential of AI and ML in the field of diabetes management and prediction	Prediction, and management of diabetes

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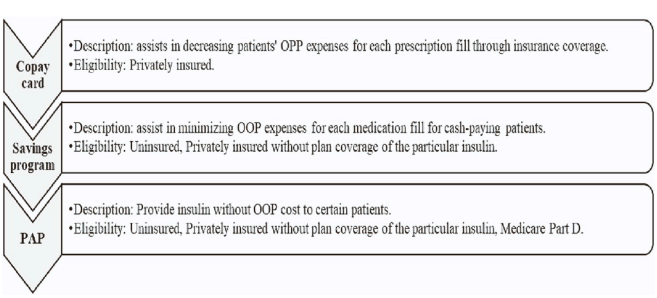

Fig. 10. Varieties and eligibility criteria of manufacturer-sponsored programs aimed at reducing insulin cost sharing [163].

Table A1 (*continued*)

Study	Provided overview	Categorizing point
Gautier et al. [41]	Potential of AI in understanding and managing diabetes including AI and understanding risk factors; AI and improving diagnosis; AI and understanding diabetes pathophysiology; AI and understanding the natural history of diabetes; and AI and managing diabetes	Prediction, diagnosis, and management of diabetes
Broome et al. [42]	Policy implications of AI and ML in diabetes management	Management of diabetes
Fatima and Pasha [43]	ML algorithms for disease diagnostic, emphasizing the importance of computer aided diagnosis in medical imaging and the need for accurate diagnostic systems to avoid misleading medical treatments	Diagnosis of diabetes
Donsa et al. [44]	Personalization of diabetes therapy using computerized DSS and ML	Management of diabetes
Burnside et al. [45]	AI and ML in optimizing insulin dosing strategies and developing personalized prediction tools	Optimize insulin usage/delivery
Thomsen et al. [46]	ML methods used for basal insulin dose guidance supporting titration of people with T2D	Optimize insulin usage/delivery
Vettoretti et al. [47]	AI methodologies and CGM sensor utilization for decision support in advanced T1D management	Optimize insulin usage/delivery
Forlenza [48]	AI and automated decision support to improve diabetes outcomes using multiple daily injections therapy	Optimize insulin usage/delivery
Makroum et al. [49]	Potential of ML and smart devices in managing diabetes and predicting postprandial glycemic status and adapting the delivery of insulin bolus	Predicting glucose levels Optimize insulin usage/delivery
Dankwa-Mullan et al. [50]	AI-powered tools and technologies, such as automated retinal screening, patient self-management tools, glucose sensors, and insulin pumps	Predicting glucose levels Optimize insulin usage/delivery
Li et al. [51]	AI in diabetes education and management	Education
Zale and Mathioudakis [52]	Clinical evidence for the role of ML models in predicting hospitalized patients' glucose trajectory	Predicting glucose levels
Alhaddad et al. [53]	ML algorithms in non-invasive blood glucose monitoring using wearable sensors	Predicting glucose levels
Mujahid et al. [56]	ML techniques for hypoglycemia prediction in diabetic patients	Predicting hypoglycemia
Tyler and Jacobs [57]	Computational and AI based decision support systems (DSSs) for managing T1D	Predicting hypoglycemia Optimize insulin usage/delivery
Ellahham [58]	AI in revolutionizing the diagnosis and management of diabetes	Diagnosis and management of diabetes Predicting diabetes complications
Kavakiotis et al. [59]	How ML and data mining techniques have been used in predicting and diagnosing diabetes, studying diabetic complications, exploring the genetic background and environment of the disease, and improving healthcare and management for diabetes patients	Prediction, and diagnosis of diabetes Predicting diabetes complications
Abhari et al. [60]	Use of various AI techniques, and how they in T2D care including disease probability prediction, screening, diagnosis, treatment guidance, and complication management	Utilizing various ML techniques /AI tools in diabetes research.
Singla et al. [61]	ML and AI in the management of chronic diseases, specifically diabetes	Utilizing various ML techniques /AI tools in diabetes research.
Indoria and Rathore [62]	ML techniques in the classification of diabetes and cardiovascular diseases	Utilizing various ML techniques /AI tools in diabetes research.
Rigla et al. [63]	Transformation of diabetes management with the addition of CGM and insulin pump data	Utilizing various ML techniques /AI tools in diabetes research.

Table A2
Separation of C1 category into clinical issues and their respective technical solutions.

Clinical issues	Technical solutions
Difficulty in achieving precise glycemic control with standard methods, varying patient responses to insulin treatment.	Developing nonlinear models using techniques like LASSO, RF, and Gradient Boosting Trees considering blood glucose dynamics and relevant features for insulin injection modeling to enhance glycemic control.
Limitations in blood glycemic control with formulaic and closed-loop methods and achieving stable blood glucose levels within desired ranges.	Implementing RL models for personalized insulin care policies integrating individualized health reward functions into the model, allowing dynamic adaptation to change in the patient's environment.
Existing costly and limited in accessibility of insulin delivery systems.	Developing an IoT-based insulin delivery system with ML algorithms to automate insulin drug delivery.
Challenges in estimating insulin requirements for hospitalized patients.	Applying ML approaches for precise estimation of insulin requirements, training models on HER data to forecast inpatient total daily insulin doses more accurately than conventional guidelines.
Difficulty in accurately predicting a patient's insulin dose, affecting overall glycemic management causing hypo/hyperglycemic episodes.	Utilizing ML models like RNN and ANN for insulin dose prediction, training models on patient data to predict optimal insulin doses based on various parameters.
Difficulty in determining optimal insulin dosage, lacking adaptability to inter- and intra-patient variability in insulin needs leading to suboptimal glucose control.	Developing automated insulin delivery systems using ML to adaptively manage insulin delivery and insulin dosage titration
Variability in individual responses to rapid-acting insulin after meals.	Developing ML-based systems for automated meal detection and carbohydrate content estimation and utilizing algorithms to analyze real-time data and adjust insulin delivery based on meal-related information.
Inconsistent postprandial glucose control leading to fluctuations in blood sugar levels (hyperglycemia or hypoglycemia), impacting overall glycemic management.	Applying ML approaches such as clustering algorithms to identify distinct patient classes based on insulin responses.

Table A3
Separation of C2 category into clinical issues and their respective technical solutions.

Clinical issues	Technical solutions
Difficulty in predicting self-care behaviors and achieving glycemic control	Utilization of supervised ML algorithms to predict self-care behaviors and glycemic control based on patient features.
Challenges in accurately forecasting glucose levels while considering limitations in resource consumption.	Assessment of ML-based prediction methods to improve accuracy and manage resource consumption in glucose forecasting.

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Table A3 (*continued*)

Clinical issues	Technical solutions
Understanding the influence of various nutritional factors on short and middle-term blood glucose levels.	Investigation through ML methods to analyze the impact of carbohydrates, proteins, lipids, fibers, and energy intake on predicting blood glucose levels.
Difficulty in accurately predicting blood glucose levels and insulin sensitivity for personalized glycemic control and Challenges in predicting longitudinal alteration in glycemic control	Implementation of explainable AI methodologies to study the impact of specific input features like pre-prandial blood glucose values, insulin dosage, and meal-related nutritional factors on blood glucose prediction and insulin sensitivity.
	Development of a mixed-effect ML framework that effectively utilizes temporal heterogeneous, sparse, and varying-length patient characteristics in predicting longitudinal alteration in glycemic control.
Understanding the overall condition of blood glucose regulation in T2D patients receiving outpatient care.	Exploration of combining an EN with ML algorithms to improve the prediction of diabetic blood glucose control.

Table A4
Separation of C3 category into clinical issues and their respective technical solutions.

Clinical issues	Technical solutions
Identifying key determinants for commencing insulin therapy in individuals with T2D	Utilization of transparent ML techniques (e.g., Logic Learning Machine - LLM) to discern crucial factors like elevated HbA1c levels, prolonged disease duration, and cardiovascular history, aiding in accurate prediction of insulin initiation.
Predicting the factors leading to the adoption of insulin pumps among T2D patients	Employing ML algorithms to identify significant predictors such as age, gender, presence of comorbidities, and medication regimens, providing insights into the factors driving insulin pump initiation in T2D cohorts.
Assessing the efficacy of ML models in determining the initiation of insulin treatment by diabetes specialists	Evaluating ML models' predictive performance, where algorithms trained on specialists' judgments' database are compared against non-specialists' decisions during initial consultations, offering insights into the predictive capabilities of ML in guiding treatment initiation decisions for T2D individuals.

Table A5
Separation of C5 category into clinical issues and their respective technical solutions.

Clinical issues	Technical solutions
Detection of missed once-daily basal insulin injections in T2D patients.	Applying ML algorithms based on CGM data used to identify adherence to basal insulin injections considering the combination of expert-dependent and automatically learned features.

Table A6
Separation of C6 category into clinical issues and their respective technical solutions.

Clinical issues	Technical solutions
Predicting and preventing nocturnal hypoglycemia in T1D patients undergoing multiple dose insulin therapy.	Utilizing ML algorithms for prediction and prevention of nocturnal hypoglycemia; Population and personalized models designed with various data sources, optimization metrics, and mitigation measures.
Real-time hypoglycemia prediction in T1D patients.	Employing feature-based ML models for real-time hypoglycemia prediction.
Identifying predictors of hypoglycemia and other outcomes in treated people with T2D.	Applying ML models to analyze structured data from a large administrative claims database to identify predictors of hypoglycemia and other clinical and economic outcomes in T2D patients.
Predicting metabolic outcomes in individuals with T2D during Ramadan.	Utilizing ML models to predict metabolic outcomes in T2D individuals fasting during Ramadan.
Developing a predictive model for hypoglycemia risk in T2D patients using basal insulin treatments.	developing a predictive model using advanced analytical methods, including ML, to analyze EHR data and identify subgroups at lower risk of hypoglycemia with basal insulin treatments and predict cost savings.
Predicting postprandial hypoglycemia.	Applying efficient ML algorithm for predicting postprandial hypoglycemia using unique data-driven features derived from the data.
Developing an insulin hypoglycemia reduction system for T1D patients.	Using ML algorithms to predict hypoglycemia and generates bolus reduction suggestions for subjects with T1D undergoing multiple insulin injections and monitoring capillary glucose levels.

Table A7
A summary of the reviewed papers of C1 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Daskalaki et al. [86]	T1D	AC learning	Patient-specific parameters	Personalized insulin infusion rate for each patient	Time spent in hypoglycaemia: 0.27 % 95.66 %: with meal uncertainty 93.02 %: with meal uncertainty and insulin sensitivity
Malmasi et al. [85]	–	SVM, LR, and Naïve Bayes	Sentence-level Information	Determining the presence/ absence of a patient refusing insulin	RNNs achieved the highest accuracy ML techniques Manually designed rule-based system on

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Table A7 (*continued*)

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
					Canary platform reached the highest accuracy.
Mosquera-Lopez et al. [70]	T1D	ANN	CGM data for detecting meals and carbohydrate estimates	Insulin dosing recommendations	Sensitivity (sens): 83.3 % False discovery rate: 16.6 % Mean detection time: 25.9 min
Jemima Jebaseeli et al. [76]	T1D	CatBoost	Patient-specific parameters	Predicting the glucose to recommend the insulin dosage	An average accuracy: 98.79 % Sensitivity: 99.83 % Specificity (spec): 99.59 %
Coales et al. [72]	T1D	Two step clustering	Clinical and biochemical characteristics	Categorize individuals within diabetes into subcategories	Low serum patients after subcutaneous injection may be associated with increased insulin resistance
Indragandhi et al. [78]	–	Decision tree, LR, and RF	Information from mobile app and hardware (infusion pump system)	Amount of insulin to be supplied	Linear regression results are better than Decision tree and RF algorithm
Gupta and Jiwani [73]	–	RNN, LSTM, ANN	Patient-specific parameters	Prediction of the patient's future insulin levels	Accurately predict the patient's future insulin levels
Peiró [81]	T1D	–	glycemia, time in range %, above range%, below range %, hypoglycemia%, high glucose blood index and low glucose blood index	Insulin infusion rate	Compared to multiple daily injections therapy, the hybrid closed-loop AP system reduces: -Periods above and below ranges by 70.7 % and 67.2 % -Hypoglycemia by 91.2 % (HGBI by 67 % and -LGBI by 73.8 %)
Noaro et al. (2021)	T1D	LASSO, RF, and GBT	Patient-specific parameters	Estimated IB dose	RF and GBT models outperformed the linear LASSO. GBT's RMSE: 0.98 U and RF's RMSE: 1.11 U.
Liu et al. [84]	T1D & T2D	SVM and RF	Patient-specific parameters	Glucose and the amount of insulin ordered in the next 24 h	Predictions of average daily glucose levels (Mean Absolute Error (MAE) 21 mg/dL, R2 0.4) and whether glucose levels will be higher than the clinically desired range in the next day (sens 0.73, spec 0.79)
Levy-Loboda et al. [75]	T1D	Decision tree, RF, SVM, KNN, and TPF	Physiological and demographic characteristics, insulin pump and its paired CGM	Whether or not an insulin dose manipulation has occurred	Overdose is easier to detect than underdoes, and the adult vs. pediatric model performs better in detecting overdose compared to other granularity models.
Fujihara et al. [101]	T2D	LR and ANN	Patient-specific parameters	Whether to initiate insulin	AUCs, accuracy, and recall of logistic regression were higher
Nguyen et al. [77]	T1D & T2D	SuperLearner (an ensemble consisting of regularized regression, RF, and GBT)	Patient-specific parameters, insurance status, creatinine, diet, counts of microbiology lab orders, and amount of glucocorticoid use within the previous 48 h	1) Whether a patient will require >6 units of total daily dose of insulin, and 2) a point-value for insulin dose is predicted	An area under the ROC: 0.85 Area under the precision-recall curve: 0.65
Noaro et al. [79,80]	T1D	MLR and LASSO	Glucose rate-of-change, Carbohydrate intake, Insulin on board, Carbohydrate ratio, Mealtime insulin bolus calculated by the standard formula	Calculated mealtime insulin bolus	The LASSO regression with an extended feature-set produced the best results.
Guzman Gómez et al. [82]	T1D	ANN, Bayesian networks, SVM, and RF	clinical variables	Estimated basal insulin dose for each of the 24 h in a day	RF can be effectively utilized to predict the basal insulin dose
de Farias and Bessa [74]	T1D	ANN	Blood glucose concentration, excluding non-measurable variables related to insulin dynamics and glucose metabolism, and food intake	Insulin dosage to be administered	Effective in handling inter- and intrapatient variability and regulating insulin infusion without requiring information about food intake.
Chen et al. [71]	T2D	XGBoost, SVM, neural network, LR, LASSO, and RF	Patient-specific parameters	Insulin titration dosage	The XGBoost algorithm showed consistent and superior performance with an RMSE of 1.30 U and Spearman's correlation coefficient of 0.982.
Annuzzi et al. [89]	T1D	Feed-Forward Neural Network	Glycemic values, insulin bolus, carbohydrates, proteins, fibers, lipids, energy	Postprandial blood glucose values at 15, 30, 45, and 60 min	Information about nutritional factors can be significant for middle-term postprandial blood glucose level predictions

Table A8
A summary of the reviewed papers of C2 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Ngufor et al. [97]	T2D	Longitudinal supervised learning: mixed-effect	Baseline patient characteristics, current HbA1c, and medication use.	Predict longitudinal change inHbA1c measured one, two,	predicting glycemic change at the 1st, 2nd, 3rd, and 4th clinical visits in advanced was 1.04, 1.08,

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Table A8 (*continued*)

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
		machine learning approach		three, and four encounters in the future	1.11, and 1.14 times that of the gradient boosted model
Xie and Wang [95]	T1D	SVM, RF Regression, GBR, MLPR, LSTM, and TCN	Physiological data, life-event data reported, and glucose measurements	Predicted blood glucose level for a given time step	DL models, vanilla LSTM network and TCN, performed better.
Wang et al. [94]	T2D	EN, RF, SVM, and back propagation ANN	Basic information, biochemical indices, and diabetes-related data	Simulate and predict blood glucose status	The EN and ML models had higher sens and accuracy than the logistic regression models.
Rodríguez-Rodríguez et al. [98]	T1D	ARIMA, RF, and SVM	Historical glucose measurements form the FGM sensor	Predicted glucose level at a future time point	Monitoring interstitial glucose data for a brief duration and employing a reduced sampling frequency result precise short-term predictions.
Kurdi et al. [87]	T1D	Multivariable LR, RF, KNN	Baseline HbA1c, CGM, carbohydrates, recommended insulin bolus dose, and sex	Meeting glycemic control of HbA1c <7.5 %	RF model showing better calibration.
Zafar et al. [88]	–	KNN, RF, LSTM, SVM, XGBoost	–	Predicting glucose profiles	LSTM's MAE: 2.50 mg/dL, ARIMA's MAE: 4.94 mg/dL, LSTM's RMSE: 3.7 mg/dL, ARIMA's RMSE: 7.67 mg/dL
Tarumi et al. [91]	T2D	SVM, and LR	Age, gender, laboratory tests (HbA1c, sodium, low-density lipoprotein (LDL), total protein, fasting glucose, triglycerides, estimated glomerular filtration rate (eGFR), vital signs (body weight, systolic blood pressure, diastolic blood pressure)	Likelihood of reaching a treatment target, such as achieving control of HbA1c to <7.0 %, within a three-month timeframe.	Models using WA and CD achieved higher prediction performance.
Miller et al. [93]	T1D	ARMA, LSTM, Static simulator and DTD-Sim	CGM data, insulin pump data, meal logs, and activity data	Forecasted blood glucose levels	AR and LSTM models are less sensitive to bolus doses and full meals. LSTM model is influenced by a large meal but not a bolus insulin dose. DTD-sim model is sensitive to bolus insulin and meals, but more stable than the static simulator.
Nagaraj et al. [165]	T2D	EN regularization-based generalized linear model, SVM, RF	Patient-specific parameters	Predicted HbA1c responses	EN regularization-based generalized linear model is better.
Benyó et al. [96]	–	DNN based methods, specifically classification DNN and Mixture Density Network	insulin sensitivity at time t	the predicted SI(t + 1) value, which represents the insulin sensitivity at the next time step	The DNN-based methods' prediction accuracy was the same or better than the currently used stochastic model.
Szabó et al. [92]	–	Two neural networks: classification deep network and mixture density network	Demographic information, and clinical variables	Predicted insulin sensitivity of the patients	Sex-specific models can enhance insulin sensitivity prediction. All AI-based prediction models outperformed the currently used 1D prediction method.

Table A9
A summary of the reviewed papers of C3 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Hankosky et al. [100]	T2D	Conditional logistic regression and penalized conditional logistic regression	Demographic characteristics, clinical, medication-use, healthcare resource utilization related variables	Main factors associated with insulin pump initiation	Consistent predictors of insulin pump initiation included CGM use, visiting an endocrinologist, acute metabolic complications, higher count of HbA1c tests, lower age, and fewer diabetes-related medication classes
Musacchio et al. [99]	T2D	Logic learning machine	Demographic factors, such as age, sex, BMI, HbA1c levels, duration of diabetes, and history of cardiovascular disease	Whether or not a patient would initiate insulin therapy within one year	Accuracy: 0.87 Sens: 0.76 Spec: 0.78 Precision of 0.91
Fujihara et al. [101]	T2D	Logistic regression and neural network	Patient-specific parameters	Whether to initiate insulin therapy	AUCs, accuracy, and recall of logistic regression were higher.

Table A10
A summary of the reviewed papers of C5 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Thyde et al. [113]	T2D	CNN, logistic regression, and multilayer perceptron	CGM data	Whether a patient is adherent or non-adherent to their insulin regimen	Mean accuracy based on learned features: 79.7 % Mean accuracies based on expert-engineered and learned features: 79.7 % and 79.8 %

Table A11
A summary of the reviewed papers of C6 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Ogunyemi and Kermah [166]	T2D	RUSBoost and adaptive boosting (AdaBoost).M1	Patient data, including demographic information, medical history, and eye exam results	A prediction of whether or not the patient has diabetic retinopathy	Accuracy:73.5 % Sens: 69.2 % Spec: 55.9 % AUC: 0.72
Bader Alazzam et al. [167]	T1D & T2D	Optimum-Path Forest and the Restricted Boltzmann Machine	Retinal images obtained from patients suspected of having diabetic retinopathy.	Classified the images as either having DR or not	RBM-1000 model had the best overall performance (accuracy: 89.5 %), RBM-500 model was superior in the automatic detection of signs of DR (sens: 100 %)
Tsao et al. [168]	T2D	Decision trees, SVM logistic regression, and ANN	Patient-specific parameters	Predict the presence or absence of diabetic retinopathy	SVM model achieved the best prediction performance AUC: 0.839 Accuracy: 0.795 Sens: 0.933 Spec: 0.724

Table A12
A summary of the reviewed papers of C8 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Sevil et al. [169]	–	KNN, SVM, naive Bayes, decision tree, ANN, linear discrimination, ensemble learning, and DL with LSTM	Reconciled signals include time-domain features, frequency-domain features, and statistical features (e. g. mean, standard deviation, skewness, kurtosis, energy, entropy, and spectral centroid)	Classification of physical states and the estimation of energy expenditure	LSTM-DL's accuracy: 94.8 % Ensemble learning algorithm's accuracy: 93.2 %.

Table A13
A summary of the reviewed papers of C7 category.

Study	Type of diabetes	ML algorithm(s)	Input(s)	Output(s)	Finding(s)
Seo et al. [119]	T1D & T2D	RF, SVM-LN or SVM-RBF, KNN, and logistic regression	glucose dynamics data collected during daytime and nighttime activities including CGM data, rate of increase of glucose, and glucose rate of change	Binary classification of hypoglycemia or non-hypoglycemia	The best-performing model was the SVM-RBF (AUC of 0.89 and F1 score of 0.70)
Mueller et al. [116]	T2D	Hypothesis-free, Bayesian ML analytics platform (GNS Healthcare REFSTM: Reverse Engineering and Forward Simulation)	Patients' medical, prescription drug, laboratory, and eligibility information (e. g., medical claims, pharmacy claims, laboratory data)	Predicted patients at high risk, who accounted for a significant proportion of hypoglycemic events	Comorbid conditions, prior hypoglycemia, anemia, insulin use, and sulfonylurea use were identified as risk factors for hypoglycemia. (ML model's AUC: 0.77)
Parcerisas et al. [114]	T1D	ANN, multinomial naïve Bayes, AdaBoost, SVM, LDA, and LSTM	CGM data, interstitial glucose concentrations, meal estimations, IB doses, and self-monitoring blood glucose measurements; data from the wristband including heart rate signal, steps performed, estimation of calories burned, and sleeping period	Prediction of nocturnal hypoglycemia events	The LSTM algorithm outperformed other algorithms in terms of accuracy, sens, and spec.
Dave et al. [115]	T1D	RF and Gradient Boosting	CGM data	Whether a patient is at risk of experiencing hypoglycemia	RF's sens: 91 % False positive rate: 8–10 %.
Elhadd et al. [117]	T2D	LR, RF, SVM, XGBoost, and DL	Physical activity data (mean and standard deviation of physical activity), time-related features (hour of the day, day of the week, part of the day), a binary indicator for Ramadan vs. non-Ramadan day, demographic information, and medication information from EHR	1) A binary classification (e.g., predicting whether a patient will experience hypoglycemia or not), 2) continuous value prediction (e.g., predicting the blood glucose level)	The best performing model was the XGBoost model (R^2: 0.837, MAE: 17.47)

Table A14
Dataset utilization across reviewed studies.

Study	Used dataset
Daskalaki et al. [86]	1) A virtual patient cohort generated by the UVA/Padova T1D simulator, which consisted of 100 adult patients, 2) a clinical dataset consisting of 20 T1D patients who were treated with insulin pump therapy.
Ngufor et al. [97]	OptumLabs Data Warehouse (OLDW) which is a large administrative claims database of commercially-insured and Medicare advantage beneficiaries across the US.
Mosquera-Lopez et al. [70]	1) An in silico dataset obtained from validated T1D simulators, 2) a real-world large dataset from 150 closed-loop participants from the Tidepool big data donation program.
Ogunyemi and Kermah [166]	Clinical data from urban safety net clinics and public health data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) consisting class imbalance.
Bader Alazzam et al. [167]	73 patients (122 eyes) who were suspected of DR and underwent ophthalmological examination and retinal scans.
Jemima Jebaseeli et al. [76]	Dataset of insulin drug analysis - STARR (STAnford Research Repository)
Sevil et al. [169]	Collected data from a multi-sensor wristband during five different physical states, including resting, activities of daily living, running, biking, and resistance training of 25 subjects (12 male and13 female) who participated in a subset of the physical activities during the experiments.
Coales et al. [72]	Two previously published randomized controlled trials (RCTs) to apply their ML approach. The RCTs were registered on clinicaltrials.gov with the registration numbers NCT02595658 and ISRCTN40811115.
Xie and Wang [95]	OhioT1DM dataset, which was released under a Data Use Agreement (DUA no. D201804) between Ohio University and Pennsylvania State University.
Seo et al. [119]	Retrospective CGM data from 104 people who had experienced at least one hypoglycemia alert value during a three-day CGM session using the Samsung Medical Center.
Indragandhi et al. [78]	University of California, Irvine ML repository
Gupta and Jiwani [73]	UCI repository dataset, which is publicly available at https://archive.ics.uci.edu/ml/datasets/diabetes containing two types of diabetes patient records: one from programmed electronic recording systems and the other from paper records
Peiró [81]	1) In-silico data generated by computer simulation to validate the comparison results between multi-daily injection and closed-loop AP, 2) in-vivo data collected from T1D patients to train and test the ML hybrid closed-loop algorithm using Accu-Chek smart pix software to collect 4.621 glycemia tests.
Wang et al. [94]	Collected data from 2787 consecutive participants recruited from 27 centers in six cities in North China between January 2016 and December 2017.
Rodríguez-Rodríguez et al. [98]	Data collected from a wearable Abbott Freestyle Libre FGM sensor combined with a smartphone to transmit data to a central server for processing. The FGM sensor has local memory that can store past measurements for up to 8 h. 25 patients are considered during 2018 under the supervision of the Endocrinology Departments of the Morales Meseguer and Virgen de la Arrixaca Hospitals, in the city of Murcia (Spain).
Kurdi et al. [87]	Using institution's HER data collection of patients (≥18 years old) on insulin pump therapy for at least six months and a follow-up visit within six months of insulin pump initiation at the clinic between December 2012 and July 2017.
Tsao et al. [168]	Collected data from a group of regular outpatients lasting for at least one year extracted for one season selected randomly from the "DM shared care" database in a private hospital in northern Taiwan
Noaro et al. (2021)	UVA/Padova T1D Simulator to generate the dataset consisted of data from 100 subjects. The use of a simulation environment allowed for testing the impact of multiple insulin bolus doses on patient blood glucose while maintaining the same conditions for each subject.
Zafar et al. [88]	OpenAPS Data Commons is a collection of anonymized diabetes data that includes rich CGM data, insulin delivery information from insulin pumps, user-entered information such as carbohydrate entries or temporary target changes, as well as algorithm-derived information about insulin dosing decisions.
Hankosky et al. [100]	Collected data from the IBM MarketScan commercial databases between 2015 and 2020 which contain individual-level de-identified healthcare claims from employers, health plans, hospitals, and Medicare and Medicaid programs across the US.
Mueller et al. [116]	De-identified health claims data from Optum Clinformatics Data Mart, which includes medical, prescription drug, laboratory, and eligibility information for over 13 million patients annually covered the period from 2014 to 2017.
Bosnyak et al. [118]	Optum's Humedica EHR data sets are selected due to their attributes, including sample size, US geographic scope, richness of clinical data (especially clinical notes via NLP), and data quality.
Musacchio et al. [99]	Electronic records of 1.5 million patients seen at clinics within the Italian Association of Medical Diabetologists between 2005 and 2019
Miller et al. [93]	Observational measurements from two T1D participants using a CGM and an insulin pump throughout daily life collected using Apple's HealthKit framework.
Parcerisas et al. [114]	Collected data from 10 patients that were monitored for 12 weeks. The clinical trial was conducted at the Hospital Clinic de Barcelona and has been registered under the identifier NCT03711656 at ClinicalTrials.gov.
Liu et al. [84]	EHR data from STARR (STAnford Research Repository).
Dave et al. [115]	CGM datasets were obtained from 112 patients using Dexcom G6 CGM devices over a range of 90 days consisting of over 1,639,921 CGM values under normal living conditions.
Oviedo et al. [120]	1) Real patient data from a cohort of 10 individuals, 2) CGM data from 10 virtual patients generated using the UVA/Padova T1D simulator.
Levy-Loboda et al. [75]	Time-series data collection consists of 225,780 clinical logs, collected from real insulin pumps and CGMs of 47 patients with T1D (13 adults and 34 children) from two different clinics at Soroka University Medical Center in Beer-Sheva, Israel over a four-year period.
Thyde et al. [113]	In-silico CGM data were generated to simulate a cohort of T2D patients on once-daily insulin injection (Tresiba).
Nagaraj et al. [165]	GIANTT database includes prescription data, medical history, results of routine laboratory tests, and physical examinations from over 50,000 patients diagnosed with T2D.
Fujihara et al. [101]	Japan Diabetes Clinical Data Management (JDDM) study group dataset consisting of data extracted from patients prescribed hypoglycemic agents from December 2009 to March 2015
Shifrin and Siegelmann [83]	Data samples from the Diabetes Control and Complications Trial (DCCT) and its follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study supplied by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repositories.
Nguyen et al. [77]	EHR data from a tertiary academic medical center from 2008 to 2020.
Noaro et al. [79,80]	Simulated dataset generated using the UVA/Padova T1D Simulator to create synthetic data for 100 virtual adult subjects.
Elhadd et al. [117]	A dataset from 13 patients with T2D who fasted during Ramadan, consisting of CGM and physical activity data including 19,540 samples. The patients were on multiple glucose-lowering therapies including insulin, with a median age of 51 years, median BMI of 33.2 kg/m2, and median HbA1c of 7.3 %.
Benyó et al. [96]	A dataset of patients treated by the Stochastic-TARgeted (STAR) protocol between June 2016 and August 2019 at Christchurch Hospital, New Zealand.
Szabó et al. [92]	In-silico validation simulating the treatment of 171 virtual patients.
Guzman Gómez et al. [82]	Data from 56 patients with T1D over 18 years using Medtronic 640G and Paradigm Veo insulin infusion pumps coupled to CGM using Enlite sensor and with an acceptable glycemic control, defined by a range of HbA1c between 6 % and 8 % and sensor use >80 % were included.
de Farias and Bessa [74]	In silico analysis using 20 virtual patients for a period of 7 days, with and without prior basal therapy, while in the long-term simulation, 1 virtual patient was assessed over 63 days
Chen et al. [71]	HER data of hospitalized T2D patients who received subcutaneous insulin injection. A total of 3275 patients with 38,406 insulin dose counts.
Malmasi et al. [85]	HER data of adult th diabetes under primary care within the networks of Massachusetts General Hospital and Brigham & Women's Hospital spanning the period from 2000 to 2014
Tarumi et al. [91]	EHR data from one healthcare system, University of Utah Health (UUH), and one health information exchange, the Indiana Health Information Exchange (IHIE)
Annuzzi et al. [89]	AI4PG dataset provided by the Diabetes Outpatient Clinic of Federico II University Hospital (Naples, Italy) and CGM public dataset DirectNet

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